A novel, long-lived, and highly engraftable immunodeficient mouse model of mucopolysaccharidosis type I.

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Public Summary:
Mucopolysaccharidosis type I (MPS I) is an inherited alpha-L-iduronidase (IDUA, I) deficiency in which glycosaminoglycan (GAG) accumulation causes progressive multisystem organ dysfunction, neurological impairment, and death. Current MPS I mouse models, based on a NOD/SCID (NS) background, are short-lived, providing a very narrow window to assess the long-term efficacy of therapeutic interventions. They also develop thymic lymphomas, making the assessment of potential tumorigenicity of human stem cell transplantation problematic. We therefore developed a new MPS I model based on a NOD/SCID/Il2rgamma (NSG) background. This model lives longer than 1 year and is tumor-free during that time. NSG MPS I (NSGI) mice exhibit the typical phenotypic features of MPS I including coarsened fur and facial features, reduced/abnormal gait, kyphosis, and corneal clouding. IDUA is undetectable in all tissues examined while GAG levels are dramatically higher in most tissues. NSGI brain shows a significant inflammatory response and prominent gliosis. Neurological MPS I manifestations are evidenced by impaired performance in behavioral tests. Human neural and hematopoietic stem cells were found to readily engraft, with human cells detectable for at least 1 year posttransplantation. This new MPS I model is thus suitable for preclinical testing of novel pluripotent stem cell-based therapy approaches.

Scientific Abstract:
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